adverse events. T cells could be engineered to have enhanced persistence or to be resistant to hostile microenvironments. Likewise, the optimum position of CAR T-cell therapy in relation to existing therapies—whether CAR T cells are best employed in frank relapse or to deepen remission, whether as a bridge to transplant or a standalone treatment—needs to be defined. Such questions can only be answered in larger, well designed studies in defined patient cohorts. More broadly, while drawing attention to the potential of CAR T-cell therapy, CD19 is a unique and ideal target antigen, and whether suitable targets can be identified to extend this approach to other cancers remains to be seen. Nonetheless, this approach is without question the most significant therapeutic advance in acute lymphoblastic leukaemia for a generation, and might represent the beginning of a new era of engineered T cells for cancer therapy.

*Persis J Amrolia, Martin Pule*
University College London Institute of Child Health, London WC1N 1EH, UK (PJA); and University College London Cancer Institute, London, UK (MP)
persis.amrolia@gosh.nhs.uk

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# The struggle of carotid artery stenting

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In *The Lancet*, Leo Bonati and colleagues[1] describe the results of the International Carotid Stenting Study (ICSS), a randomised controlled trial comparing carotid artery stenting and carotid endarterectomy. I compliment the authors for completing the largest trial of these two revascularisation strategies in patients with symptomatic carotid disease. In this primary analysis in 1713 patients, the main finding was that, at a median follow-up of 4·2 years, the incidence of the primary endpoint—any fatal or disabling stroke—was virtually identical in the two groups; the difference between the groups was only three events (52 *vs* 49). Beyond 30 days from the procedure, stenting and endarterectomy were similar in terms of prevention of any ipsilateral stroke (hazard ratio [HR] 1·29, 95% CI 0·74–2·24). Nevertheless, an excess of any stroke was observed in the stenting group, with a 5-year cumulative risk of 15·2% compared with 9·4% in the endarterectomy group (HR 1·71, 95% CI 1·28–2·30), although functional disability and quality of life did not differ between groups. This finding is not unexpected, because an interim ICSS analysis reported an increased periprocedural stroke rate in the stenting group (HR for any stroke at 120 days after randomisation 1·92, 95% CI 1·27–2·89).[2]

Meta-analyses of randomised trials suggest that, in the periprocedural phase, patients allocated to stenting have a significant excess of minor strokes, whereas patients undergoing endarterectomy have significantly more myocardial infarctions and cranial nerve injuries.[3] In patients younger than 70 years, 30-day rates of stroke and death are similar after stenting and endarterectomy, and in the long term the rates of death or disabling stroke are similar for the two procedures at all ages.[4]

The excess of periprocedural strokes has limited the acceptance of stenting as an alternative to

endarterectomy. Attention has been drawn to the fact that in four of the six major randomised trials (ie, those that enrolled more than 300 patients) of carotid stenting versus endarterectomy, interventionists with a lifetime experience of as few as ten carotid stenting procedures were included, and that for operators who did not meet this minimum requirement, tutor assistance was provided.[5] In trials of endarterectomy compared with medical management done more than a decade earlier, the entry criteria for surgeons were much more stringent. For example, in the Asymptomatic Carotid Atherosclerosis Study (ACAS),[6] all endarterectomies performed at a candidate centre's affiliated hospitals in the previous year were assessed. Once the centre was deemed to be qualified, each potential surgeon who wished to participate was required to submit the results of his or her 50 most recent consecutive endarterectomies. In ICSS, 38 CAS stenting procedures were aborted because of difficulty gaining access to the carotid stenosis compared with only two endarterectomy procedures, which might be interpreted as a marker of inadequate expertise, selection of patients, or both.[2]

In their discussion, Bonati and colleagues[1] argue against the hypothesis that insufficient endovascular expertise skewed trial outcomes. First, they point out that there were no differences in event rates between centres supervised by tutors and those with experienced operators. Second, they note that even in larger centres the outcomes favoured endarterectomy. The definition of an experienced operator in ICSS, however, was a lifetime case-load of at least 50 stenting procedures, of which ten or more had to have been in the carotid artery.[2] Additionally, larger centres were defined by the enrolment of 50 patients or more in the trial, which corresponds to a minimum average inclusion of ten patients per year. Finally, Bonati and colleagues quote a pooled analysis of three randomised trials, including ICSS, which concluded that stenting outcomes were not altered by the lifetime endovascular experience of the operators.[7] Accordingly, no difference was noted in patient outcomes after stratification for tertiles of lifetime stenting experience of the operators at the time of the procedure (0–16 cases, 17–37 cases, and more than 37 cases).[7] Although from a methodological point of view the conclusion is sound, it needs to be underlined that two-thirds of the patients in these trials were treated by operators with lifetime experience of 37 carotid stenting interventions or fewer at the time of the procedure.

No further studies randomly allocating symptomatic patients to carotid stenting or endarterectomy are in sight, although ECST-2 (ISRCTN97744893) should allow an indirect comparison between these two procedures. In asymptomatic patients, some information, albeit non-conclusive, should become available from the ACT-1 trial (NCT00106938), which has completed enrolment of around 1600 patients who were randomised 3:1 to stenting or endarterectomy. The ACST-2 study (NCT00883402) aims to recruit 5000 asymptomatic patients, but no results will be available for several years. Finally, the SPACE-2 (ISRCTN 78592017) trial, which is continuing, and CREST-2 (NCT02089217), for which enrolment should start by the end of 2014, will also allow only indirect comparisons between carotid stenting and endarterectomy in asymptomatic patients. On the basis of the current randomised evidence and this perspective with respect to new trials, the future of carotid stenting is uncertain.

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*Marco Roffi*
Division of Cardiology, University Hospital, 1211 Geneva 14, Switzerland
marco.roffi@hcuge.ch

I declare no competing interests.



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